Introduction

Stem cells and their unique properties: Stem cells are special cells which not only have the ability of self-renewal but can also be a lifelong source of specialised functional cells of different human organs. Development of a human embryo into a healthy new-born child is possible because of the unique ability of embryonic stem cells to form different tissues and organs. Most adult human tissues and organs also have stem cells that can produce their functional specialised cells as and when required. The self-renewal ability of stem cells ensures that stem cells are not depleted and enough stem cells remain to produce sufficient number of specialized cells of that organ during the long human lifespan, until aging starts affecting stem cells.

Stem cells in Regenerative Medicine and human diseases: When a disease or injury causes severe depletion of the functional cells of a human organ or system, the function of that organ or organ system is lost. In the natural healing process, some organs such as skin, blood, liver etc. can often regenerate its form and function by producing sufficient numbers of new functional cells from the stem cells present in them. However, specialized cells of some organs like the nerve cells in the brain, spinal cord, eyes and muscles have limited or no capacity to regenerate and restore full function. In the last two decades, medical science has undertaken extensive research to explore the potential of stem cells from the same organ or tissue type (homologous use) or from a different organ or tissue type (non-homologous use) to restore some lost bodily function. These stem cells may be from the same person (autologous source) or from another person (allogeneic source). Research to regenerate the form and function of a human organ or organ system from stem cells or tissue engineering is called 'Regenerative Medicine'.

Status of Stem cells in Regenerative Medicine and human diseases: Unfortunately, the promise of Regenerative Medicine in general, and stem cells in particular, is yet to be realized due to several technical, biological, ethical and medical challenges. To produce sufficient number of specialised cells for restoring a lost body function with just a small number of stem cells or by using stem cells from one organ to restore cells and function of a different organ (such as mesenchymal stem cells in bone marrow or fat tissue to restore nerve or muscle function) has proven to be far more difficult in humans than what was thought based on animal experiments. As a result, the inherent appeal of stem cells has remained largely unfulfilled in human diseases. The exception is however the use of "Haematopoietic Stem Cells" for reconstituting or regenerating the bone marrow in order to start producing blood and immune cells. Transplantation of enough number of "Haematopoietic Stem Cell" in a procedure called

Bone Marrow Transplantation or Haematopoietic Stem Cell Transplantation from the same person (autologous) or from another human donor (allogenic) is a recognized medical indication of stem cell use for benign and malignant life threatening haemato-lymphoid diseases or few immune related diseases. Haematopoetic stem cells are also progenitors for other cells like osteoclasts and have successfully used in osteopetrosis and some inborn errors of metabolism like Gaucher disease, mucopolysaccharidosis. Use of other types of stem cells and even the bone marrow derived stem cells to restore function of other organs remains experimental and is subject of ongoing controlled clinical trials. Not only the efficacy of these experimental stem cell use is uncertain, the process of taking out stem cells, culturing or growing them, storing them and putting them back can cause changes in these cells and sometimes serious side effects, including some reported cases of cancers.

Why Stem cells continue to be used for debilitating or incurable conditions outside controlled research studies: A large number of controlled prospective research studies (phase I, II and III clinical trials) investigating the safety and efficacy of stem cells for different diseases have been completed or are ongoing in Europe, USA, Korea and Japan. A small number of such research studies are also being conducted in other countries, including India. All developed countries have taken a very cautious and stringent regulatory approach regarding how different types of stem cells can be procured, processed, stored and used for preclinical or clinical research or as stem cell therapy outside research studies. Participants of regulated interventional research in any field, including stem cells, are made aware through a detailed written informed consent process about the experimental nature of the therapy, unproven efficacy and uncertainty regarding the benefits and risks of stem cells, the natural history of the disease, current standard therapy for that disease and any alternative treatments. It is the duty of the research sponsors to provide free of cost medical tests and treatments done as part of stem cell clinical trial and research, including the cost of procuring, storing and using stem cells. Circumventing the route of rigorous research studies to establish the safety and efficacy of a particular type of stem cells for a specific disease or aging condition, some unlicensed or even licenced and registered medical practitioners engage in unethical practices of selling unproven stem cell therapy as a magical remedy to desperate families with incurable and potentially fatal diseases with little or no hope of cure from other methods. Desperate patients from around the world including USA and Europe with stricter enforcement of regulations for stem cell use outside clinical trials get lured to stem cell clinics in South America, China, Russia and India. The US FDA and European Medical Agency has warned against this practice through several such advisories.

https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies

https://www.fda.gov/news-events/press-announcements/statement-stem-cell-clinic-permanent-injunction-and-fdas-ongoing-efforts-protect-patients-risks

https://www.fda.gov/news-events/press-announcements/federal-court-issues-decision-holding-us-stem-cell-clinics-and-owner-adulterated-and-misbranded-stem

Is Stem cell research permitted or encouraged by the governmental agencies?

The unethical and unregulated use of stem cells as, often promoted as a magical remedy is not allowed by the government in the developed world and many Low and Middle Income Countries (LMIC) including India. However, considering the incurable nature of many diseases, and the acknowledged potential of stem cells, most countries, including India, encourage and fund scientific, ethical and regulated research in the field of stem cells. The purpose of such research is to obtain safety and efficacy data with the use of a particular type of stem cell in a particular condition. To provide guidance and to facilitate human research in stem cells, while curbing exploitation of vulnerable patients, the Indian government through the Indian Council of Medical Research (ICMR) has come out with successive National Guidelines in this field since 2007. The most recent National Guidelines for Stem Cell Research with inputs from all stakeholders including various government agencies and regulators, patients, medical and scientific experts and the industry, was released in 2017. These guidelines are revised at regular intervals to incorporate any new evidence for the safety or efficacy of stem cells.
https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf

Need for National Guidelines for evidence-based use of Stem cells as a routine or standard treatment option: In many countries including India, there is a lack of clarity among patients, and to some extent among the medical community, whether stem cell therapy can be considered as a standard treatment option for a specific medical condition or should remain as an unproven experimental approach. There are several reports of increasing use of stem cells therapy for a wide range of diseases, often with little or no scientific evidence of efficacy or cure. Unethical promotions with false claims and misleading advertisements have been widely used to promote unscientific stem cell therapy. Several instances of public exploitation and grievances from members of the public have been received by the ICMR and other government agencies from aggrieved patients describing how they were lured into unproven stem cell therapies. Often the complainants demanded actions to be taken by the regulatory agencies and professional bodies to curb such practices. With this background, the Govt. of India has entrusted the ICMR to frame guidelines on stem cell therapy.

In order to develop a scientific and unbiased guideline for evidence based use of stem cell as a routine or standard treatment option in India, the ICMR has solicited opinion from expert clinicians, professional medical societies and through its website from any clinician or member of public to submit level I or level II scientific evidence for clinical efficacy of stem cells in any

disease indications with reference for such evidence from peer reviewed Pubmed indexed medical and scientific journals.

https://icmr.nic.in/content/icmr-inviting-level-i-or-level-ii-scientific-evidence-and-grade-or-b-recommendation-use-stem

A critical review of the comments and evidence provided by medical experts and their professional societies or any member of the public and the scientific literature was done to draft guidelines and statements for evidence-based use of stem cell therapy.

Statements have been prepared for individual diseases or groups of diseases or conditions on the "EVIDENCE BASED STATUS FOR THE USE OF STEM CELLS IN (Disease condition)". In these statements the first section is for the public and patients using layman terms while the second section is for doctors, scientists and allied healthcare professionals providing major research studies in the scientific literature, scientific level of evidence and a summary recommendation based on the current scientific evidence.

International Society for Stem Cell Research (ISSCR)

The International Society for Stem Cell Research (https://www.isscr.org/) is the leading professional organization of stem cell scientists and represents over 4,000 members in 67 countries including India. Like ICMR in India, FDA in USA, EMA in Europe, this international society also felt the urgent need to address the growing public concern regarding the unscientific or unethical use of stem cell therapy. The ISSCR has also issued a statement on reporting false marketing claims and adverse events from clinics offering unapproved stem cell therapies.

https://www.closerlookatstemcells.org/patient-resources/how-to-report-false-marketing-claims-and-adverse-events-from-clinics-offering-unapproved-stem-cell-therapies/.

In parallel with the ICMR initiative and public advertisement inviting comments and evidence for stem cell use from public and medical professionals, the ISSCR has also come out with factsheets on current status of stem cell use. The ISSCR document highlights that other than Hematopoietic stem cell (also called Bone Marrow) transplant for certain haematological or immune system disorder, the "list of diseases for which stem cell treatments have been proven to be beneficial and/or have obtained regulatory approval for use is still very short" and that "some bone, skin and corneal (eye) injuries and diseases can be treated by grafting or implanting tissues in which stem cells are essential for the healing process". The ISSCR cautions that "However, clinics around the world continue to provide unproven stem cell treatments and often market them as cures for a variety of diseases and conditions without sound scientific

evidence or regulatory approval. These so-called treatments have, in some cases, caused patients great harm physically, and at great expense financially".
https://www.isscr.org/professional-resources/scientific-professional-resources/disease-fact-sheets
https://www.isscr.org/scientific-clinical-resources/disease-fact-sheetshttps://www.closerlookatstemcells.org/2020/01/14/truths-around-stem-cell-treatments/

The ISSCR concise factsheets provide the current state of stem cell science for specific diseases, including background on the disease, rationale for using cell-based therapies, evidence for specific approaches and current status of the field with respect to clinical trials. A total of 11 conditions have been covered so far.

1. Age-related macular degeneration
2. Amyotrophic lateral sclerosis
3. Chronic obstructive pulmonary disease
4. Diabetes
5. Huntington's disease
6. Liver disease
7. Multiple sclerosis
8. Myocardial infarction / Heart failure
9. Osteoarthritis
10. Parkinson's disease
11. Paediatric leukodystrophies

Evidence Based Status of Use of Stem Cells in Amyotrophic Lateral Sclerosis (ALS) Or Motor Neuron Disease (MND)

A. Information for public and patients

What is Amyotrophic lateral sclerosis (ALS) OR Motor Neuron Disease (MND)?

This is a group of progressive neuro-degenerative diseases in which the special nerve cells called Motor Neurons in the brain and spine are affected. Whenever ALS / MND is suspected, a more detailed evaluation and special tests are done by the Neurologists before making a diagnosis. As the nerve cells continue to die, the muscles supplied by these nerves are unable to function or move. As a result, the patient gradually becomes wheelchair bound and eventually when the muscles needed for breathing movement are affected, breathing becomes increasingly difficult and may be fatal. Some forms of ALS or MND can be familial and genetic testing in such cases helps to confirm this.

What is the treatment of ALS?

The current multidisciplinary management of this condition includes supportive and rehabilitative care to relieve symptoms, manage complications and improve the quality of life. Currently there are no proven treatment methods which can permanently reverse the damage to motor neurons and the resultant difficulty in movements or breathing. However this condition has variable progression and some patients can live for a longer period with good supportive care and rehabilitation.

Have stem cells been used in ALS / MND?

Along with supportive therapies and rehabilitation, few studies have reported their experience with the use of different types of stem cells for patients with ALS or MND. From the published studies, websites and other sources, it has come to our knowledge that many Indian patients with ALS/MND have been offered different types of stem cell therapies within and outside clinical trial / research. ICMR with inputs from medical specialists in this field has reviewed the existing scientific and medical literature and submissions from practicing doctors and their professional societies regarding any evidence based safety and efficacy of stem cells in ALS / MND. Critical review of the studies reported so far do not support the use of stem cell therapy over and above the behavioural and supportive therapies for ALS or MND

RECOMMENDATIONS (2021)

Based on a critical review of the available scientific evidence by the ICMR experts, stem cell therapy should NOT be offered as a standard or routine therapy to patients with ALS / MND. These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for ALS/ MND.

CAUTIONARY NOTE

From various websites and other sources, it has come to our knowledge that some doctors and clinics in India continue to offer stem cells as a standard treatment option to ALS / MND

patients outside the purview of regulated and approved clinical trials. Patients with ALS / MND from India and those coming from outside India should be aware that any type of stem cell therapy for ALS / MND should be offered only as part of ongoing clinical trials that have all the approvals from the regulatory authorities in India. These trials should follow the National Guidelines on Stem Cell Research.
(https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf). As part of regulated clinical trials, patients should be closely monitored not only for objective measures of clinical benefit but also for any possible harms with use of stem cells. As per the ICMR National Bioethics guidelines 2017.
(https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf)
clinical trial participants should have read and signed the informed consent form which explains them standard and alternative therapies, possible benefits and harms due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

B. Information for Medical / Scientific / Allied Health Professional

The diagnosis of ALS / MND is made after a detailed neurological and if required genetic evaluation. There are no established causes of ALS / MND and it is an active area of research. Patients with ALS/ MND are managed with supportive care and rehabilitation and management of complications. Along with these supportive and rehabilitative therapies, several studies have been reported on the use of stem cells in this condition. Many Indian patients with ALS/MND have also been offered different types of stem cell therapies as part of research studies and also as a standard treatment option which is outside the purview of approved clinical trial. ICMR with inputs from experts in this field has reviewed the existing scientific and medical literature and submissions from practicing doctors and their professional societies regarding level of evidence for efficacy and safety of stem cells in ALS/MND.

A critical review of the published human studies that are either randomized controlled trials or have been submitted in response to the ICMR call for Level I/II evidence supporting the use of stem cells in ALS/MND has been undertaken. Summary of some representative studies is outlined below:

Amyotrophic Lateral Sclerosis/ Motor Neuron Disease	
S.No.	**Publications and Author's conclusions or critique**
I	Stem cell treatments for amyotrophic lateral sclerosis: a critical overview of early phase trials. Goutman SA et al. Expert OpinInvestig Drugs. 2019 Jun;28(6):525-543. doi:

	10.1080/13543784.2019.1627324. Study conclusion (expert opinion): Clinical trials in humans are still in the nascent stages of development. It will be critical to ensure that powered, well-controlled trials are conducted, that optimal treatment windows are identified, and that the ideal cell type, cell dose, and delivery site and method are determined. Several trials have used more invasive procedures, and ethical concerns of sham procedures on patients in the control arm and on their safety should be considered.
ii	Advances in stem cell therapy for amyotrophic lateral sclerosis. Mazzini L et al. Expert OpinBiolTher. 2018 Aug;18(8):865-881. DOI: 10.1080/14712598.2018.1503248 Study conclusion: While data from individual studies are encouraging, stem-cell-based therapies do not yet represent a satisfactory, reliable clinical option. The field will critically benefit from the introduction of well-designed, randomized and reproducible, powered clinical trials. Comparative studies addressing key issues such as the nature, properties, and number of donor cells,the delivery mode and the selection of proper patient populations that may benefit the most from cell-based therapies are now of the essence. Multidisciplinary networks of experts should be established to empower effective translation of research into the clinic.
iii	Cell based therapies for amyotrophic lateral sclerosis/motor neuron disease S Fadilah Abdul Wahid et al. Cochrane Systematic Review - Intervention Version published: 08 November 2016 https://doi.org/10.1002/14651858.CD011742.pub2. Author's conclusion: Currently, there is a lack of high quality evidence to guide practice on the use of cell based therapy to treat ALS/MND. We need large, prospective RCTs to establish the efficacy of cellular therapy and to determine patient, disease and cell treatment related factors that may influence the outcome of cell based therapy. The major goals of future research should be to determine the appropriate cell source, phenotype, dose, and route of delivery, as these will be key elements in designing an optimal cell based therapy programme for people with ALS/MND. Future research should also explore novel treatment strategies, including combinations of cellular therapy and standard or novel neuroprotective agents, to find the best possible approach to prevent or reverse the neurological deficit in ALS/MND, and to prolong survival in this debilitating and fatal condition.
Iv	Efficacy of Stem Cell Therapy in Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis. Moura MC et al. J Clin Med Res. 2016 Apr;8(4):317-24. RESULTS AND CONCLUSIONS: A meta-analysis confirmed the efficacy of stem cell therapy in improving survival in preclinical trials, where a mean difference of 9.79 days (95% confidence interval: 4.45 - 15.14) in lifespan favoured stem cell therapy. In contrast, the number of clinical studies is still insufficient to assess their effectiveness, and these studies only demonstrate the absence of serious adverse events. However, even this conclusion should be interpreted with caution because clinical studies are retrospective & heterogeneous and have unsatisfactory quality.
V	The effect of autologous bone marrow mononuclear cell (BMNC) transplantation on the survival duration in Amyotrophic Lateral Sclerosis - a retrospective controlled study. Alok

	Sharma, **Hemangi Sane,** Amruta Paranjape et al. American J Stem Cell 2015; 4(1): 50–65. Of the 57 patients with ALS, 37 received BMNC transplantation and 20 patients did not receive and served as controls. Authors conclusion: Prospective randomized controlled studies with a larger sample size and rigorous methodology are required for conclusive findings.

Summary of Evidence and Recommendations for Medical / Scientific Professionals (2021)

Based on the review of available scientific evidence, stem cell therapy should NOT be offered as a standard or routine therapy to patients with Amyotrophic lateral sclerosis (ALS) OR Motor Neuron Disease (MND)

The experts observed that ALS/MND through rare is a progressive and fatal disease. There is therefore a need to undertake research into the causes and more effective management of ALD/MND. Since conventional management fails to significantly delay control symptoms in many cases, such families see hope in some miraculous recovery with the use of stem cells without understanding the risks versus benefit ratio. It is therefore imperative that use of any type of stem cell in ALS/MND should be restricted to clinical trials with due approval from regulatory authority in India and as per the national guidelines on stem cell research.(https://www.icmr.nic.in/sites/default/files/guidelines/Guidelines_for_stem_cell_research_2017.pdf). As part of regulated clinical trials, patients should be closely monitored not only for objective measures of clinical benefit but also for any possible harms with use of stem cells. As per the ICMR National Bioethics guidelines 2017 (https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf). trial participants should have read and signed the informed consent form which explains them alternative therapies, possible benefits as well as harm due to experimental treatments like stem cell therapy. Participants should not be made to pay for any expenses incurred beyond routine clinical care and which are research related including tests, investigations and any interventions (such as stem cells). This is applicable to all participants, including those in comparator/control groups. Participants in a clinical trial should be provided compensation in the event of any harm or permanent injury or death due to the use of experimental stem cell therapy.

These guidelines will be periodically reviewed for any new evidence showing benefit or harm with the use of stem cells for ALS/MND